CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number : 040245

Trade Name: CARISOPRODOL TABLETS USP 350MG

Generic Name: Carisoprodol Tablets USP 350mg

Sponsor : Vintage Pharmaceuticals, Inc.

Approval Date: September 8, 1997

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION 040245

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	Included	Pending Completion	Not Prepared	Not Required
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Chemistry Review(s)	X			
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Pharmacology Review(s)				
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Correspondence				

ANDA 40-245

SEP 8 1997

Vintage Pharmaceuticals, Inc.
Attention: Rebecca A. Thurman
3241 Woodpark Blvd.
Charlotte, NC 28206

Dear Madam:

This is in reference to your abbreviated new drug application dated January 24, 1997 submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Carisoprodol Tablets USP, 350 mg.

Reference is also made to your amendment dated July 23, 1997.

We have completed the review of this abbreviated application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly, the application is approved. The Division of Bioequivalence has determined your Carisoprodol Tablets USP, 350 mg to be bioequivalent and, therefore, therapeutically equivalent to the listed drug (Soma Tablets, 350 mg of Wallace Laboratories). Your dissolution testing should be incorporated into the stability and quality control program using the same method proposed in your application.

Under 21 CFR 314.70, certain changes in the conditions described in this abbreviated application require an approved supplemental application before the change may be made.

Post-marketing reporting requirements for this abbreviated application are set forth in 21 CFR 314.80-81. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

We request that you submit, in duplicate, any proposed advertising or promotional copy which you intend to use in your initial advertising or promotional campaigns. Please submit all proposed materials in draft or mock-up form, not final print. Submit both copies together with a copy of the proposed or final printed labeling to the Division of Drug Marketing, Advertising, and Communications (HFD-240). Please do not use Form FD-2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) for this initial submission.

We call your attention to 21 CFR 314.81(b)(3) which requires that materials for any subsequent advertising or promotional campaign be submitted to our Division of Drug Marketing, Advertising, and Communications (HFD-240) with a completed Form FD-2253 at the time of their initial use.

Sincerely yours,

/S/

Douglas L. Sporn
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 040245

FINAL PRINTED LABELING

EACH TABLET CONTAINS:
Carisoprodol, USP ..... 350 mg
USUAL ADULT DOSAGE: 1 tablet three times daily and at bedtime. See package insert for full prescribing information.
DISPENSE in a tight, light-resistant container as defined in the USP.
STORE at controlled room temperature 15°-30° C (59°-86° F).

NDC 0254-2410-28

CARISOPRODOL TABLETS, USP 350 mg

CAUTION: Federal law prohibits dispensing without prescription.

100 TABLETS

Vintage®

Mfg. by:
VINTAGE PHARMACEUTICALS, INC.
CHARLOTTE, NC 28206
Rev. 1/97
R1

SEP 8

N 3 0254-2410-28 7

EACH TABLET CONTAINS:
Carisoprodol, USP ..... 350 mg
USUAL ADULT DOSAGE: 1 tablet three times daily and at bedtime. See package insert for full prescribing information.
DISPENSE in a tight, light-resistant container as defined in the USP.
STORE at controlled room temperature 15°-30° C (59°-86° F).

NDC 0254-2410-35

CARISOPRODOL TABLETS, USP 350 mg

CAUTION: Federal law prohibits dispensing without prescription.

500 TABLETS

Vintage®

Mfg. by:
VINTAGE PHARMACEUTICALS, INC.
CHARLOTTE, NC 28206
Rev. 1/97
R1

SEP 8

N 3 0254-2410-35 5

EACH TABLET CONTAINS:
Carisoprodol, USP ..... 350 mg
USUAL ADULT DOSAGE: 1 tablet three times daily and at bedtime. See package insert for full prescribing information.
DISPENSE in a tight, light-resistant container as defined in the USP.
STORE at controlled room temperature 15°-30° C (59°-86° F).

NDC 0254-2410-38

CARISOPRODOL TABLETS, USP 350 mg

CAUTION: Federal law prohibits dispensing without prescription.

1000 TABLETS

Vintage®

Mfg. by:
VINTAGE PHARMACEUTICALS, INC.
CHARLOTTE, NC 28206
Rev. 1/97
R1

8

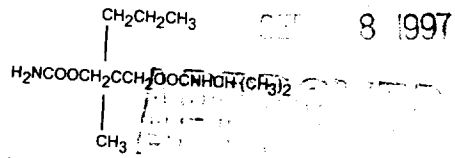
N 3 0254-2410-38 6

CARISOPRODOL TABLETS, USP

DESCRIPTION

Carisoprodol Tablets, USP are available as 350 mg round, white tablets.

Carisoprodol is (±)-2-methyl-2-propyl-1,3-propanediol carbamate isopropylcarbamate. Carisoprodol is a white, crystalline powder, having a mild, characteristic odor and a bitter taste. It is very slightly soluble in water; freely soluble in alcohol, in chloroform, and in acetone; its solubility is practically independent of pH. Carisoprodol is present as a racemic mixture. The structural formula is:



$C_{12}H_{24}N_2O_4$ MW = 260.34

Other Ingredients

Carisoprodol Tablets, USP—croscarmellose sodium, hydrogenated vegetable oil, hydroxypropyl methylcellulose, magnesium stearate and microcrystalline cellulose.

CLINICAL PHARMACOLOGY

Carisoprodol produces muscle relaxation in animals by blocking interneuronal activity in the descending reticular formation and spinal cord. The onset of action is rapid and effects lasts four to six hours.

INDICATIONS AND USAGE

Carisoprodol Tablets are indicated as an adjunct to rest, physical therapy, and other measures for the relief of discomfort associated with acute, painful musculoskeletal conditions. The mode of action of this drug has not been clearly identified, but may be related to its sedative properties. Carisoprodol does not directly relax tense skeletal muscles in man.

CONTRAINDICATIONS

Acute intermittent porphyria as well as allergic or idiosyncratic reactions to carisoprodol, or related compounds such as meprobamate, mebutamate, or tybamate.

WARNINGS

On very rare occasions, the first dose of carisoprodol has been followed by idiosyncratic symptoms appearing within minutes or hours. Symptoms reported include extreme weakness, transient quadriplegia, dizziness, ataxia, temporary loss of vision, diplopia, mydriasis, dysarthria, agitation, euphoria, confusion, and disorientation. Symptoms usually subside over the course of the next several hours. Supportive and symptomatic therapy including hospitalization, may be necessary.

Usage in Pregnancy and Lactation: Safe usage of this drug in pregnancy or lactation has not been established. Therefore, use of this drug in pregnancy, in nursing mothers, or in women of childbearing potential requires that the potential benefits of the drug be weighed against the potential hazards to mother and child. Carisoprodol is present in breast milk of lactating mothers at concentrations two to four times that of maternal plasma. This factor should be taken into account when use of the drug is contemplated in breast-feeding patients.

Usage in Pediatric Patients: Because of limited clinical experience, Carisoprodol Tablets are not recommended for use in patients under 12 years of age.

Potentially Hazardous Tasks: Patients should be warned that this drug may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks such as driving a motor vehicle or operating machinery.

Additive Effects: Since the effects of carisoprodol and alcohol or carisoprodol and other CNS depressants or psychotropic drugs may be additive, appropriate caution should be exercised with patients who take more than one of these agents simultaneously.

Precautions: Carisoprodol is metabolized in the liver and excreted by the kidney; to avoid its excess accumulation, caution should be exercised in administration to patients with comprised liver or kidney function.

Drug Dependence: In dogs, no withdrawal symptoms occurred after abrupt cessation of Carisoprodol from dosages as high as 1 gm/kg/day. In a study in man, abrupt cessation of 100 mg/kg/day (about five times the recommended daily adult dosage) was followed in some subjects by mild withdrawal symptoms such as abdominal cramps, insomnia, chilliness, headache, and nausea. Delirium and convulsions did not occur. In

clinical use, psychological dependence and abuse have been rare, and there have been no reports of significant abstinence signs. Nevertheless, the drug should be used with caution in addiction-prone individuals.

ADVERSE REACTIONS

Central Nervous System—Drowsiness and other CNS effects may require dosage reduction. Also observed: dizziness, vertigo, ataxia, tremor, agitation, irritability, headache, depressive reactions, syncope, and insomnia. (See also *Idiosyncratic Reactions* under "WARNINGS")

Allergic or Idiosyncratic Reactions—Allergic or Idiosyncratic reactions occasionally develop.They are usually seen within the period of the first to fourth dose in patients having had no previous contact with the drug. Skin rash, erythema multiforme, pruritus, eosinophilia, and fixed drug eruptions with cross-reaction to meprobamate have been reported with Carisoprodol. Severe reactions have been manifested by asthmatic episodes, fever, weakness, dizziness, angioneurotic edema, smarting eyes, hypotension, and anaphylactoid shock. (See also *Idiosyncratic Reactions* under "WARNINGS"). In case of allergic or idiosyncratic reactions to Carisoprodol, discontinue the drug and initiate appropriate symptomatic therapy, which may include epinephine, antihistamines, and in severe cases corticosteroids. In evaluating possible allergic reaction, also consider allergy to excipients (information on excipients is available to physicians on request.)

Cardiovascular—Tachycardia, postural hypotension, and facial flushing.

Gastrointestinal—Nausea, vomiting, epigastric distress, and hiccup.

Hematologic—Leukopenia in which other drugs or viral infections may have been responsible and panytopenia, attributed to phenylbutazone, have been reported. No serious blood dyscrasias have been attributed to carisoprodol.

DOSAGE AND ADMINISTRATION

Carisoprodol Tablets—The usual adult dosage is one 350 mg tablet, three times daily and at bedtime. Usage in patients under age 12 is not recommended.

OVERDOSAGE

Overdosage of Carisoprodol has produced stupor, coma, shock, respiratory depression, and very rarely, death. The effects of an overdosage of carisoprodol and alcohol, or other CNS depressants, or psychotropic agents can be additive effects, even when one of the drugs has been taken in the usually recommended dosage. Any drug remaining in the stomach should be removed and symptomatic therapy given. Should respiration or blood pressure become compromised, respiratory assistance, central nervous system stimulants, and pressor agents should be administered cautiously as indicated. Carisoprodol is metabolized in the liver and excreted by the kidney. Although Carisoprodol overdosage experience is limited, the following types of treatment have been used successfully with the related drug meprobamate: diuresis, psmotic (mannitol) diuresis, peritoneal dialysis, and hemodialysis (Carisoprodol is dialyzable). Careful monitoring of urinary output is necessary and caution should be taken to avoid overhydration. Observe for possible relapse due to incomplete gastric emptying and delayed absorption. Carisoprodol can be measured in biological fluids by gas chromatography. (Douglas, J.F. et al: J. Pharm. Sci. 58:145, 1969)

HOW SUPPLIED

Carisoprodol Tablets are white, round, unscored tablets debossed "2410 V". Carisoprodol Tablets are available in bottles of 100, 500 and 1000.

Storage: Store at controlled room temperature 15–30° C (59–86° F). Dispense in a tight, light-resistant container as defined in the USP

Caution: Federal law prohibits dispensing without a prescription.

Manufactured by:
VINTAGE PHARMACEUTICALS, INC.
Charlotte, NC 28206

IN-156
Rev 6/97
R1

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 040245

CHEMISTRY REVIEW(S)

Chem Closed

1. CHEMISTRY REVIEW NO. 2

2. ANDA #40-245

3. NAME AND ADDRESS OF APPLICANT

Vintage Pharmaceuticals Inc.
3241 Woodpark Blvd.
Charlotte, NC 28206

4. BASIS OF SUBMISSION

Accepted by OGD

5. SUPPLEMENT(s)

N/A

6. PROPRIETARY NAME

N/A

7. NONPROPRIETARY NAME

Carisoprodol

8. SUPPLEMENT(s) PROVIDE(s) FOR:

N/A

9. AMENDMENTS AND OTHER DATES:

1/24/97 - original submission
7/23/97 - amendment responding to OGD's Facsimile dated 6/23/97

10. PHARMACOLOGICAL CATEGORY

Skeletal Muscle Relaxant

11. Rx or OTC

Rx

12. RELATED IND/NDA/DMF(s)

See review #1.

13. DOSAGE FORM

Tablet

14. POTENCY

350 mg

15. CHEMICAL NAME AND STRUCTURE

See review #1.

16. RECORDS AND REPORTS

N/A

17. COMMENTS

N/A

18. CONCLUSIONS AND RECOMMENDATIONS

A. CHEMISTRY

Issues are closed.

B. LABELING

Review of 7/23/97 amendment is pending.
Satisfactory. Lee Rovnew. Brown 8/20/97

C. BIOEQUIVALENCY - satisfactory.

D. ESTABLISHMENT INSPECTION - satisfactory.

The recommendation for approval of the ANDA is dependent on a satisfactory response to labeling concerns.

19. REVIEWER:

/S/

Shirley S. Brown

DATE COMPLETED:

7/30/97

July 30, 1997

/S/

7/31/97

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 040245

BIOEQUIVALENCE REVIEW(S)

ANDA 40-245

JUN 25 1997

Vintage Pharmaceuticals, Inc.
Attention: Rebecca A. Thurman
3241 Woodpark Blvd.
Charlotte NC 28206

Dear Madam:

Reference is made to your abbreviated new drug application submitted pursuant to Section 505 (j) of the Federal Food, Drug and Cosmetic Act for Carisoprodol Tablets USP, 350 mg.

1. The Division of Bioequivalence has completed its review and has no further questions at this time.

2. The dissolution testing will need to be incorporated into your stability and quality control programs as specified in USP 23.

Please note that the bioequivalency comments expressed in this letter are preliminary. The above bioequivalency comments may be revised after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling or other scientific or regulatory issues. A revised determination may require additional information and/or studies, or may conclude that the proposed formulation is not approvable.

Sincerely yours,

/S/

Nicholas Fleischer, Ph.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

JUN 24 1997

Carisoprodol Tablets, USP	Vintage
350 mg Tablets	Charlotte, NC
ANDA #40-245	Submission Date:
Reviewer: Moo Park	January 24, 1997
Filename: 40245dw.197	

Review of Dissolution Data and a Waiver Request

I. Objective

Review of Vintage's dissolution testing data and waiver request for Carisoprodol Tablets, USP, 350 mg strength. Wallace's Soma^{R}, 350 mg tablet, was used as the reference product.

II. Background

Carisoprodol produces muscle relaxation and is indicated for the relief of discomfort associated with acute, painful musculoskeletal conditions. The usual adult dose is one 350 mg tablet, three times daily and bedtime.

III. Study Details

1. Carisoprodol Tablets, USP, is AA rated.

2. The test product does not contain any inactive ingredients that may cause a bioequivalence problem. The reference product contains the following inactive ingredients: alginic acid, magnesium stearate, potassium sorbate, starch, and tribasic calcium phosphate. The formulation of the test product is shown in Table 1.

Table 1. Test Formulation

Ingredient	Content/tablet, mg
Carisoprodol, USP	350
Microcrystalline Cellulose, NF	(b)4 - Confidential Business
Hydroxypropyl Methylcellulose, USP	
Croscarmellose Sodium, NF	
Hydrogenated Vegetable Oil, NF	
Magnesium Stearate, NF	
Total Weight	465

3. **The comparative dissolution testing data on the test and reference products met the USP dissolution specifications as shown in Table 3. The USP method and specifications are shown in Table 2 below.**

Table 2. USP Dissolution Specification for Carisoprodol Tablets

Medium and Volume	900 mL of 0.05 M phosphate buffer (pH 6.9) with 5 units of alpha-amylase/mL
Apparatus and rpm	USP 23 Apparatus 2 (paddle) at 75 rpm
Time	60 min
Tolerances	NLT (b)4 Q)

4. The waiver of *in vivo* bioequivalence requirements is granted.

IV. Recommendations

1. The Division of Bioequivalence agrees that the information submitted by Vintage demonstrates that its Carisoprodol Tablets, USP, 350 mg strength, falls under 21 CFR 320.22 (c) of the Bioavailability/ Bioequivalence Regulations. The waiver of an *in vivo* bioequivalence study for the test product is granted. The test product is deemed bioequivalent to Wallace's Soma® Tablets, 350 mg strength.

2. The dissolution testing data conducted by Vintage on its Carisoprodol Tablets, USP, 350 mg strength, lot #075046, are acceptable.

3. **The dissolution testing should be incorporated into the firm's manufacturing controls and stability program. The** dissolution testing should be conducted in 900 mL of 0.05 M phosphate buffer (pH 6.9) with 5 units of alpha-amylase/mL at 37 °C using USP 23 Apparatus 2 (paddle) at 75 rpm. The test products should meet the following specifications:

> **Not less than (b)4 of the labeled amount of the drug in the dosage form is dissolved in 60 minutes.**

The firm should be informed of the recommendations.

/S/

Moo Park, Ph.D.
Chemist, Review Branch III
Division of Bioequivalence

RD INITIALED RMHATRE
FT INITIALED RMHATRE

/S/ 6/18/97

Ramakant M. Mhatre, Ph.D.
Team Leader, Review Branch III
Division of Bioequivalence

Concur: /S/ Date: 6/24/97

Nicholas Fleischer, Ph.D.
Director
Division of Bioequivalence

cc: ANDA #71-185 (original, duplicate), Park, Drug File, Division File, HFD-650 (Director)

File history: Draft (5/21/97); Final (6/17/97)

Table 3. *In Vitro* Dissolution Testing Data	
I. General Information	
Drug Product (Generic Name)	Carisoprodol Tablets
Strength	350 mg
ANDA Number	40-245
Applicant	Vintage
Reference Drug Product	Wallace's Soma[R] Tablets, 350 mg strength
II. USP Method for Dissolution Testing	
Medium and Volume	900 mL of 0.05 M phosphate buffer (pH 6.9) with 5 units of alpha-amylase/mL
Apparatus and rpm	USP 23 Apparatus 2 (paddle) at 75 rpm
Time	60 min
Tolerances	(b)4 - Confidential
Assay Method	

III. Dissolution Data (%)

Time	Test Product Lot No: 075046 Strength: 350 mg No of Units: 12			Reference Product Lot No: 6B1019A Strength: 350 No of Units: 12 Exp: 1/2001		
Min	Mean	Range	%CV	Mean	Range	%CV
10	75.5	(b)4 - Confidential Business	1.0	68.1	(b)4 - Confidentia Business	5.4
20	91.9		0.7	86.1		1.1
30	96.9		1.1	93.9		1.3
45	98.4		0.4	97.5		1.7